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Drug therapies for post menopause urinary incontinence

This article provides an update on drug therapies for the treatment of urinary incontinence in post menopause women. The recommendations are based on the updated guidelines from the National Institue for Health and Care Excellence (NICE), 2013a). Where the recommendations within the guidelines have not changed from the 2006 version the original has been referenced.

Urinary Incontinence (UI) is defined as “the complaint of any involuntary leakage of urine” (Abrams et al, 2010). As women age, the combination of physical disabilities, co-morbidities, pregnancies and childbirth and the physiological effects of declining oestrogen levels put post menopausal women at risk of urological dysfunction, which can lead to incontinence.

UI is commonly reported by women of all ages, with a wide range of severity and nature of symptoms. Although not life threatening, the symptoms can have a serious impact on the physical, psychological and social well being of individuals. It is estimated that 9.6 million women are affected by bladder problems in the UK (Hunskaar et al, 2004). A review of 36 population studies from 17 countries undertaken by the International Continence Society in 2004 found that prevalence estimates for UI ranged from 5% (Van Oyen and Van Oyen, 2002) to 69% (Swithinbank, et al, 1999), with most studies reporting rates between 25% to 45% (Abrams et al, 2010).

Most women experience the menopause between 45 and 55 years (Lee, 2009). The average rate of UI amongst post-menopausal women is 23.5% (Irwin et al, 2006 and Milsom et al, 2001) with older women at an increased risk of pelvic floor dysfunction (Maclennan et al, 2000) and more likely to have mixed and urge incontinence (Diokno et al,1986, Molander et al, 1990 and Roberts et al, 1998).

Due to the embarrassing symptoms of UI many women do not seek help (Shaw et al, 2006) Although dated, a study by Sadler (1996) reported that 42% of women affected by UI symptoms waited up to 15 years before seeking help. It is therefor important that health professionals take every oportunity when they come into contact with women (for example at routine screeing visits) to ask about any bladder symptoms they may be experiencing.

Treatment options available for UI depend on the type of symptoms and underlying pathology, and include conservative measures suchas pelvic floor exercises, pharmacological therapy and surgery. Health professionals must be able to inform patients of all the options available to them for the treatment and management of their condition to ensure that patients have the opportunity to make informed decisions (NICE, 2013a).

Normal bladder function

The bladder has two main functions: to store and expel urine. Remaining continent relies on a balance of urethral sphincter closure and detrusor sphincter muscle activity. In storage, urethral closure pressure should exceed the pressure from detrusor contractions. Any increases in intra-abdominal pressure (such as when sneezing or coughing) are transmitted to the urethra and bladder equally, resulting in continence. Normal voiding is achived when urethral pressure falls and bladder pressure rises (Getliffe and Dolman, 2007).

Storage and voiding are controlled by the autonomic and somatic nervous systems. The detrusor muscle is a layer of bladder wall made of smooth muscle fibres. As the bladder stretches during filling, sympathetic nerves cause the detrusor to relax and the internal sphincter to contract. To initiate voiding the parasympathetic nervous system is triggered to contract the detrusor and relax and open the internal sphincter. This relaxation and opening of the internal sphincter is under

voluntary control (see figure 1). Problems with this mechanism and the muscles can lead to incontinence.

Age related changes in women

Maintaining continence partly relies on the urethral mucosa providing a watertight seal. Muscle mass generally decreases in older women, with a deterioration of 5% per decade. Perucchini (2002) noted a 3% per year reduction in urethral striated muscle mass in older people. The average age for a women to reach the menopuase is 51 years (Lee, 2009). Urogenital tissue is dependent upon oestrogen stimulation to mainatin normal strcuture and function. Oestrogen receptors can be found in the vagina, vulva, urethra and bladder neck (Blakeman et al, 2001 and Goldstein, 2010). The physiological effects of the menopause result in a decline in circulating oestrogen, potentially leading to urogynaecological dysfunction including urgency, frequency, dysuria, incontinence and recurrent urinary tract infections (American College of Obstetricians and Gynaecologists Women's Healthcare Physicians, 2004 and MacLennan, 2000). The reduction in oestrogen also increase the risk of atrophic vaginitis. Atrophy or inflammation of the vagina can lead to decreased strength in the pelvic floor muscles, as well as vaginal discomfort, burning, itching and associated dyspareunia (Goldstein, 2010). Urge incontinence is more common in post-menopausal women, and in particular those with a history of diabetes, hysterectomy and tow or more urinary tract infections in the previous year (Walker, GJA and Gunasekera, P, 2011).

Arthritis is strongly associated with urge incontinence, which could be secondary to mobility problems ir an autoimmune interaction that creates urge type symptoms (Jackson et al, 2004). Several factors can have a role in age related incontinence, such as impaired mobility and cognitive state, as well as environmental considerations such as toilet access (McGrother et al, 1998)

Receptors and neurotransmitters

Many drug therapies for urinary incontinence are based on targeting the neurotransmitters required for voiding. Coordination of voiding involves four principle neurotransmitters: glutamate, serotonin, noradrenaline and acetylcholine. The parasympathetic neurons and somatic nerves use acetylcholine as a primary neurotransmitter, whereas, noradrenaline is used in sympathetic neurons (Abrams et al, 2010).

Acethycholine acts on muscarinic and nicotinic receptors. When stimulated, the preganglionic nerves releases acetycholine at the ganglion, which in turn stimulates the nicotinic receptors of postganglionic neurons. This releases acetycholine to stimulate the muscarinc receptors of the target organ. The binding of acetycholine to muscarinic receptors results in the contraction of bladder (Abrams et al, 2010).

Relaxation of the bladder smooth muslce is induced by the release of noradrenaline by the sympathetic fibres. Within the base of the baldder is a large concentration of $alpha_1$-adrenergic receptors, which, when activated by noradrenaline produce smooth muscle contraction, which enhances the muscle tone of the bladder neck, urethral smooth muscle, straited external urethral sphincter and pelvic floor muslce, thus maintinaing continence. The somatic axons in the pudendal nerve also release acetycholine, which activate nicotinic receptors producing a contraction of the external sphincter straited muscle (Abrams et al, 2010).

Glutamate is thought to be the principle neurotransmitter within the spinal cord, activating acetycholine relsease which stimulates the nicotinic receptors in the striated urethral sphincter. It is thought that this action is enhanced by serotoninin and noradrenaline (Abrams et al, 2010).

There are five types of muscarinic acethycholine receptor isotopes, specialised to different tissues and functions within the body. M2 receptors are the most common muscarinic acetycholine receptor type found within the detrusor. However, M3 receptors within the bladder smooth muscle are thought to be the most important for inducing bladder contraction. The detrusor also contains a small number of $beta_3$-adrenoreceptors, which may facilitate muscle relaxation when activated by noradrenaline during bladder filling (Abrams et al, 2010).

Assessment

Before considering treatment options a preliminary assessment i.e. history taking and physical examination should be undertaken to exclude the need for specialist referral and categorise the women's urinary incontinence as stress incontinence (SI), mixed urinary incontinence (UI), or urgency UI /overactive bladder (OAB) (NICE, 2013a). Initial treatment should be started on the basis of this assessment, with treament directed to the predominant symptom where mixed UI is present. The preliminary assessment (usually undertaken in primary care) should include:

- A bladder diary completed for a minimum of 3 days. It is good practice for these 3 days to cover an variations in their usuial activities such as working and leisure time.
- A routine digital assessment of the pelvic floor, to ascertain pelvic floor muscle strength and contraction
- A urine dipstick test to detect the presence of blood, glucose, protein, leucocytes and nitrites in the urine – treat symptomatic urinary tract infections (those presenting with urgency and frequency) with antibiotics and then reassess urgency and frequency symptoms before initiating further pharmacological treatment.
- Measure post-void residual volume by bladder scan for women with symptoms which suggest voiding dysfunction or recurrent UTI. Although an in and out catheter can be used in the absence of a bladder scan, the scan should be used in preference to catheterisation as this is less invasive and a lower incidence of adverse events.
- Symptom scoring and quality of life assessment
- A functional assessment – including toilet access and ease of using aids
- Bowel dysfunction – faecal incontinence or constipation

Urinary incontinence can also be a side effect of some medications and consideration should also be taken of current use of cconcomitant drugs – including ACE inhibitors, diuretics, some anti-depressants, hormone replacement therapy (HRT), anti-psychotics, cholinesterase inhibitors, opioids, sedating anti-histamines, sedatives and hypnotics, which disrupt the normal storing and passing of urine or increase the amount of urine produced (Porter and Kaplan, 2011).

Specialist referral

Women with UI who present with any of the following should be urgently referred (NICE, 2006) microscopic haematuria in women aged 50 years and older

- visible haematuria
- recurrent or persisting UTI associated with haematuria in women aged 40 years and older
- suspected malignant mass arising from the urinary tract.

Women with UI and the following symptoms should also be considered for referral to a specialist service (NICE 2006):

- persisting bladder or urethral pain

- clinically benign pelvic masses
- associated faecal incontinence
- suspected neurological disease
- symptoms of voiding difficulty
- suspected urogenital fistulae
- previous continence surgery
- previous pelvic cancer surgery
- previous pelvic radiation therapy
- women who are found to have a palpable bladder on bimanual or abdominal examination after voiding.

Treatment options

Before considering pharmacological treatments, conservative management techniques, such as caffeine restriction, modification of high or low fluid intake, bladder training including time delayed voiding, pelvic floor muscle training and the use of a bladder diary should be tried as these can provide relief from the symptoms of urinary incontinence. Conservative therapies have been proven to be effective strategies and in motivated patients can be more effective than medication (NICE, 2013a). The updated NICE guideline (2013a) retains the recommendation that bladder and pelvic floor re-training should be offered to women with urgency or mixed UI for a minimum of 3 months as first line treatment. If following a 3 month period of first line non pharmacological treatments, symptoms have failed to resolve then drug therapy may be initiated, however it is important to note that bladder re-training and the non-pharmacological methods should continue alongside any drug treatment.

Treatment and care should respect the patient's individual needs and preferences. Professionals should form a partnership with patients enabling them to make informed decisions and choices. This also aids in improving concordance and reducing medication waste (NICE, 2009).

Pharmacological options for the management of urinary incontinence

Overactive bladder

The term overactive bladder (OAB) relates to symptoms if urgency with or without urinary incontinence, but usually with frequency and nocturia (Abrams et al, 2010) When overactive bladder occurs with incontinence it is refered to as "overactive bladder wet"; in the absence of incontinence it is refered to as "overactive bladder dry" (Haylen et al, 2010). An overactive bladder is characterised by the involuntary contraction of the detrusor muscle during bladder filling (Abrams et al, 2010)

Where conservative measures are insufficient or ineffective pharmacological treatment should be considered. Drugs with an antimuscarinic or anticholinergic action remain the mainstay for the treatment and management of overactive bladder (NICE, 2013a). Anticholinergic medications inhibit the binding of acetycholine on the muscarinic receptors within the detrusor. This decreases the bladder (detrusor) contractions without inhibiting normal voiding, thus the ability of the bladder to store urine is increased and the frequency and urgency symptoms are reduced. The action and metabolism of the different anticholinergic medications varies depending on the affinity to a particular muscarinic or nicotinic receptor. Anticholinergic medications are associated with common adverse side effects such as constipation, dry mouth, blurred vision and somnolence. More serious

side effects include cardiac and cognitive events (Robinson and Cardozo, 2012). Older women will be more susceptable to central nervous system effects, which include cognitive disturbances such as sedation, inability ot concentrate, memory impairment and delirium. This high rate of adverse effects is associated with porr concordance, with a reported discontinuation rate between 43-83%, with over half never fulfilling the initial prescription (Sexton et al, 2011). As anticholinergic drugs undergo hepatic metabolism involving cytochrome P450 isoenzymes (in particular CYP3A4 and CYP2D6) and renal excretion, care should be taken in women with renal or hepatic impairment. There is also a risk of postural hypertension. Concommittant use of other medications with anticholinergic properties such as antihistamines, may increase the risk of side effects (Robinson and Cardozo, 2012). As a result of the increased adverse effect lower doses should always be considered in older women.

Before commencing any OAB drug treatment, prescribers must discuss with women:

- the likelihood of success and associated common adverse effects,
- the frequency and route of administration,
- that some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect,
- that they may not see the full benefits until they have been taking the treatment for 4 weeks.
- Adjustment of doses or a change of drug may be necessary depending on their response

(NICE, 2013a)

There are a number of different anticholinergic drugs licensed for OAB treatment within the UK. NICE (2013a) recommends that:

oxybutynin (immediate release, IR),

or tolterodine (immediate release, IR),

or darifenacin modified release (MR) (once daily preparation),

are the first choices for women with OAB or mixed UI.

If the first treatment for OAB or mixed UI is not effective or well-tolerated, another drug with the lowest acquisition cost should be offered (NICE, 2013a). Second line antimuscarinic drugs include fesoterodine, tropsium chloride and popiverine.

Flavoxate, propantheline or imipramine should not be used for the treatment of UI or OAB in women. When prescribing for women with concomitant neurological disease prescribers should refer to NICE Guidance CG148 (2012) . Duloxetine should not be used in the treatment of OAB.

Oxybutinin hydrochloride

Oxybutynin has a mixed action as anticholinergic and direct muscle relaxant. Oxybutinin is available in immediate release (IR), modified release (MR) and transdermal patch formulations (Joint Formulary Committee, 2014). Oxybutinin is well absorbed in the gastrointestinal system and extensively metabolised by the cytochrome P450 system and has a high affinity for muscarinic receptor in the bladder (Andersson et al, 2009).

Immediate release oxybutynin is associated with a high risk of common side effects, and as such should be commenced at low doses initially. Oxybutinin IR should not be offered to frail older

women with, for example, multiple co-morbidities, functional impairment or those with dementia or cognitive impairment (NICE, 2013a). In this patient group Tolterodine IR is considered first line option.

Although the use of modified release oxybutynin may improve tolerability this effect has not been proven. The recommendation that patients are prescribed 5mg daily increasing by 5mg per week up to maximum of 20mg daily is considerably more expensive than using immediate release oxybutynin and is not recommended by NICE (2013a) first line.

Transdermal oxybutynin patches should be offered to women who are unable to tolerate oral medication (NICE, 2013a). But it should be noted that side effects and poor tolerance including skin irritation remain a possibility (Dmochowski et al, 2003).

Tolteradine

Tolteradine is a competitive muscarinic agonist with no selectivity for the muscarinic receptors in the bladder. Tolteradine is rapidly absorbed and metabolised by the cytcochrome P450 system (Andersson et al, 2009). It is thought to have functional selectivity for the bladder over the salivary glands (Stahl et al, 1995), therefore generally better tolerated than oxybutynin, due to the lower risk of dry mouth (Madhuvrata et al, 2012), and does not require dose titration (NICE, 2013a). However, although there were lower discontinuation rates in patients taking tolterodine, patients were less likely to be continent after 4 weeks. The use of modified release (MR) tolterodine may offer a lower incidence of dry mouth and may be suitable for patients who require once daily preparations. Tolteradine MR is not considered cost effective by NICE (2013) and therefore not recommended first line.

Darifenacin

Darifenacin is well absorbed in the gastrointestinal system and extensively metabolised by the cytochrome P450 system (Andersson et al, 2009). It has relative selectivity for M3 receptors. Haab, Stewart and Dwyer (2004), reported a good cardiac and central nervous system safety profile, with few cognitive side effects, making this a good choice in older women. Darifenacin can interact with with CYP2D6 inhibitors and CYP3A4 inhibitors (fluconazole, grapefruit juice, erythromycin) and others.

Solifenacin

Solifenacin is well absorbed in the gastrointestinal system and extensively metabolised by the cytochrome P450 system and has moderate selectivity for M3 over M2 receptors (Andersson et al, 2009). Although solifenacin demonstrates greater efficacy than tolteradine, it also has a higher incidence of side effects in particular constipation (Chapple, 2005). Solifenacin is also associated with interactions with CYP3A4 inhibitors such as ketoconazole.

Mirabegron

Mirabegron is a ß$_3$-adrenoceptor agonist, which activates beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and store urine. It has a lower place in therapy and relatively weak evidence due to limited comparative data with other anti-muscarinics and limited long- term efficacy data. NICE (2013b) recomends mirabegron as an option for treating people for whom antimuscarinic drugs are contra-indicated, clinically ineffective or they have experienced unacceptable side effects. Dosage adjustments are required with renal and hepatic impairment and concomitant treatment with CYP3A inhibitors (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin). Other cautions in

prescribing include Digoxin, Type 1c anti-arrythmics (flecanide, propafenone) and tricyclic anti-depressants (imipramine, desimipramine).

Tropsium chloride

Tropsium chloride has no selectivity for muscarinic receptor subtypes. It is not metabolised by the cytochrome P450 system, and is expected to cross the blood-brain barrier only to a limited extent, which results in fewer negative cognitive side effects, which can make it a useful choice in older women (Widemann, Fusgen and Hauri, 2001).

Fesoterodine

Fesoterodine is metabolised in the liver and has a selective affinity to M3 receptors. Fesoterodine has well documented efficacy and an acceptable adverse event profile (Andersson et al, 2009).

Propiverine Hydrochloride

Propiverine Hydrochloride is rapidly absorbed and has a large first pass effect. It has a combined antimuscarinic and calcium antagonistic action (Tokuno., Chowdhury and Tomita, 1993).Propiverine has no selectivity for muscarinic receptor subtypesand the role of the calcium antagonistic component is not established (Andersson et al, 2009).

Oestrogens

For older women intravaginal oestrogen therapy can provide some improvement in the symptoms of UI especially in post-menopausal women with vaginal atrophy (Panay et al, 2013, Cody et al, 2009 and NICE, 2013a). Intravaginal oestrogen has an effect on the bladder and urethral epithelium and may help relieve symptoms of urinary frequency, urgency and possibly reduce recurrent urinary tract infections (Panay et al, 2013)

Systemic oestrogen or hormone replacement therapy is contraindicated in the treatment of urinary incontinence due to the association with systemic side effects such as thromboembolism and stroke and may in fact increase the likelihood of developing urinary incontinence (Panay et al, 2013 and NICE, 2006).

Botulinum toxin

First line invasive intervention for OAB is multiple injections of botulinum toxin (type A) directly into the bladder detrusor muscle every 6-12 months. Botulinum toxin (type A) is a neurotoxin that inhibits the release of acetylcholine from the presynaptic cholinergic nerve ending, which decreases the muscle contractibility owing to localized chemical denervation (Nitti et al; EMBARK Study Group, 2013 and Andersson et al, 2009). Botulinum toxin type A has been shown to reduce urinary symptoms of OAB by 35-50% compared with placebo (NICE, 2013a). Botox is reserved for women with more severe incontinence that affects their quality of life, which has not reposnded to conservative tharpy including drug management. One of the main side effects is that the toxin can paralyse the bladder, leading to large residual urine volumes. Around 20% of patients will need to perform self catheterisation, therefore all women who are offered botulinum toxin injections must be willing and able to undertake self-catheterisation prior to the procedure (NICE, 2013a)

Desmopressin

Desmopressin is a synthetic analogue of vasopressin or antidiuretic hormone, which inhibits diuresis, while avoiding vasopressive effects (NICE, 2013). When given at night it reduces

nocturnal urine production (nocturia). NICE (2013) recommend desmopressin, may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom. Particular caution should be taken when prescribing for women with cystic fibrosis. The prescribing of desmopressin should be avoided in women over 65 years with cardiovascular disease or hypertension (NICE, 2013).

Stress Urinary Incontinence (SUI)

SUI is the "complaint of involuntary leakage on effort or exertion, or on sneezing or coughing" (Abrams et al, 2010). Evidence suggests that the urethra is hormonally sensative with oestrogen providing an advantagous effect (Blakeman, 2001).

Treatment of (SUI)

The mainstay of treatment for SUI remains pelvic floor exercises and lifestyle options such as weight loss (NICE, 2006).

Duloxetine

Duloxetine remains the only drug currently licensed for the treatment of SUI (Joint Formulary Committee, 2014). Duloxetine is a serotonin and noradrenaline reuptake inhibitor that acts mainly in the spinal cord to increase pudendal nerve activity, which increases urethral sphincter closure pressure within the storage phase (NICE, 2006). Duloxetine is associated with a high incidence of adverse effects which include nausea, dry mouth and constipation, as such it also has a high discontinuation rate (NICE, 2006). NICE (2013a) recommend Duloxetine as a second line therapy for women only if surgery is declined or unsuitable.

Conclusion

Drug therapy can play an important role in the treatment and management of urinary incontinence in post-menopausal women. Clinicians need to ensure when considering medication as an option that they include the women in a prescribing partnership, which insures that they are fully informed of the potential benefits and side effects. Particular care should be taken when prescribing for older women with concomitant conditions and medications due to the increased risk of interactions and side effects in this group of patients. For some patients, a trial of more than one drug may be required before an appropriate option is found and patients should be informed of this, to avoid disillusionment with their care.

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